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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SEHARASEYON, JEGATHEESAN	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 12/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/813,329	CARROLL ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-47 and 50-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-47 and 50-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/1//2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/19/2004 has been entered. An action on the RCE follows.

2.Claims 48 and 49 have been cancelled. Claims 41, 50, 51, 52, 58, 62, 63, 64 and 66 have been amended. Therefore, Claims are 41-47 and 50-66 are pending.

3. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101,withdrawn

4. The rejection of claims 41-47 and 50-66 under 35 USC 101 for lack of utility is withdrawn in response to Applicants arguments and the declaration filed under rule 132 on 6/01/2004 pointing to apoptotic effect of the instant invention as possible utility.

Claim Rejections - 35 USC § 112, first paragraph, withdrawn

4. The rejection of claims 41-47 and 50-66 under 35 USC 112, first paragraph for lack of enablement due to the lack of utility, as set forth in Paper No.11 and 15 is withdrawn in response to Applicants arguments and the declaration filed under rule 132 on 6/01/2004 pointing to apoptotic effect of the instant invention as a possible utility.

5. The rejection of claims 41, 46, 50, 51, 58-60 and 64-66 under 35 USC 112, first paragraph lack of written description because the written description is not

commensurate with recitation of 41, 46, 50, 51, 58-60 and 64-66, as set forth in Paper No.11 and 15 is withdrawn in response to Applicants amendments and arguments.

6. The rejection of claims 41, 46, 50, 51, 58-60 and 64-66 under 35 USC 112, first paragraph because the claims were not enabling, as set forth in Paper No.11 and 15 is withdrawn in response to Applicants amendments and arguments.

Claim Rejections - 35 USC § 102(b), withdrawn

7. The rejection of claims 41, 51, 58 and 62 under 35 USC 102(b), as being anticipated by Celinker et al. (AC005974, 1988), as set forth in Paper No.11 and 15 is withdrawn in response to Applicants amendments and arguments. Applicants correctly point to the fact the instant invention describes apoptotic activity that is not present in Celinker reference. Thus the rejection is withdrawn.

Claim Rejections - 35 USC § 112,, withdrawn

8. The rejection of claims 41, 58, 62, 63 and 66 under 35 USC 112, second paragraph for being vague and indefinite, as set forth in Paper No. 15 is withdrawn is response to Applicants amendments and arguments.

9. The rejection of claims 62, 63 and 66 under 35 USC 112, first paragraph because the claims were not enabling, as set forth in Paper No. 15 in response to Applicants amendments and arguments.

10. New claim objections and rejections necessitated by Applicants amendments.

Claim Objections

11. Claim 41 is objected to because of the following informalities: The word "complimentary" (see parts d and e) is spelled incorrectly. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

12. Claims 41, 50, 51, 52, 56, 58, 60,62, 63 and 66 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12a.Claims 41, 58, 62 and 66 are rejected as being vague and indefinite in the recitation of the term "tissue". Art teaches that apoptosis are induced in cells and not in tissues (see also page 156, line 25- of the specification). Claims 42-47 50-57, 59-61 and 63-65 are rejected insofar as they depends claim 41.

12a. Claim 52 is rejected as being vague and indefinite in the recitation of the phrase ".....vector comprising the isolated nucleic acid molecule of a member of the group consisting of claim....". It is suggested that Applicants re write the as follows: ".....vector comprising a member of the group consisting of the isolated nucleic acid molecule of claim...". Claims 53 and 54 are rejected insofar as they depends claim 52.

12b. Claim 53 is rejected as being vague and indefinite in the recitation of the term "sequences". A recombinant host cell typically comprises a single vector sequence for expression purposes. Claiming a single vector sequence can obviate the rejection. Claim 54 is rejected insofar it they depends claim 53.

12c. Claim 62 is rejected as being vague and indefinite in the recitation of the term "deletions". It is unclear if Applicants are contemplating a single deletion or multiple deletions.

Claim Rejections - 35 USC § 112, first paragraph

13. Claims 41, 58, 61 and 63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

The specification discloses nucleotides of SEQ ID No: 5, nucleotide encoding SEQ ID No: 6. This disclosure meets the written description and enablement provisions of 35 USC 112, first paragraph. However, the specification does not disclose any other nucleotides which hybridize to a nucleic acid comprising the nucleotide sequence of SEQ ID No: 5 or fragments of SEQ ID NO: 5 or nucleotides encoding a protein comprising the amino acid of SEQ ID No: 6 or nucleotide encoding polypeptide fragments consisting of SEQ ID NO: 6 and also comprising nucleotides encoding a polypeptide that induces apoptosis in a cell or tissue. The specification also does not disclose any other nucleotides which is at least 80.0% identical to the nucleotide sequence of SEQ ID No: 5 or fragments of SEQ ID NO: 5 or nucleotides encoding a protein comprising the amino acid of SEQ ID No: 6 or nucleotide encoding polypeptide fragments consisting of SEQ ID NO: 6 or sequences containing deletion or substitutions and also comprising nucleotides encoding a polypeptide that induces apoptosis in a cell

or tissue. The claims as written, however, encompass various nucleotide sequences which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 41, 48, 61 and 63. The specification does not provide written support for the genus encompassed by the instant claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*See Vas-Cath* at page 1116).

With the exception of the isolated nucleotide sequence of SEQ ID No: 5, nucleotide sequence encoding SEQ ID No: 6 the skilled artisan cannot envision all the detailed chemical structures of the claimed nucleotide sequences, regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only an isolated nucleotide sequence of SEQ ID No: 5, nucleotide sequence encoding SEQ ID No: 6 but not the full breadth of the claims encompassing the various fragments meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. As a result, it does not appear that the inventors

were in possession of the various polynucleotide sequences set forth in claims 41, 48, 61 and 63.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

14. Claims 41, 48, 61 and 63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for an isolated nucleotide sequence of SEQ ID No: 5, nucleotide sequence encoding SEQ ID No: 6 does not reasonably provide enablement for all possible nucleotide sequences that hybridize to a nucleic acid comprising the nucleotide sequence of SEQ ID No: 5 or fragments of SEQ ID NO: 5 or nucleotide sequence encoding a protein comprising the amino acid of SEQ ID No: 6 or nucleotide sequence encoding polypeptide fragments consisting of SEQ ID NO: 6 and also comprising nucleotides encoding a polypeptide that induces apoptosis in a cell or tissue. The specification is not enabled for any other nucleotide sequence which is at least 80.0% identical to the nucleotide sequence of SEQ ID No: 5 or fragments of SEQ ID NO: 5 or nucleotides encoding a protein comprising the amino acid of SEQ ID No: 6 or nucleotide encoding polypeptide fragments consisting of SEQ ID NO: 6 or sequences containing deletion or substitutions or the various modifications contemplated by the Applicant and also and comprising nucleotides encoding a polypeptide that induces

apoptosis in a cell or tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Despite knowledge in the art for producing fragments of a given polypeptide with amino acid deletions, insertions or substitutions the specification fails to provide any guidance regarding the changes/modifications contemplated and yet retain the function of the all-possible variations or fragments with activity or modifications claimed in the instant invention. Furthermore, detailed information regarding the structural and functional requirements of the disclosed protein is lacking. Although it is accepted that the amino acid sequence of a polypeptide determines its structural and functional properties, predicting a protein's structure and function from mere sequence data remains an elusive task. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein like the ability of the polypeptide or polypeptide fragment to induces apoptosis in a cell or tissue is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative

substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495, the references previously provided in the Office Action of 01/28/2003). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions and yet contain the apoptotic activity. Although the specification outlines art-recognized procedures for producing and screening for active variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation to identify variants that contain the apoptotic activity. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Therefore, predicting which nucleotide sequence encoding the variants would retain the functions of the DmTNF protein is well outside the realm of routine experimentation. Thus, undue amount of experimentation would be required to generate changes/modifications of the nucleotides contemplated and yet retain the function of the DmTNF variant proteins claimed.

Applicants have not taught how one of skill in the art would use the full scope of polynucleotide sequences encompassed by the invention of claims 41, 48, 61 and 63. The specification as filed does not sufficiently teach one of skill in the art how to make and/or use the full scope of the claimed sequences. The amount of experimentation required to make and/or use the full scope of the claimed sequences would require trial and error experimentation to determine the functional sequences. Given the breadth of claims 41,48, 61 and 63 in light of the unpredictability of the art as determined by the lack of working examples and shown by the prior at of record, the level of skill of the artisan, and the lack of guidance provided in the instant specification, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

15. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the

Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JS 12/04

JANET ANDRES
PRIMARY EXAMINER